

(iv) The preparation contains not more than 1 percent of biphenamine hydrochloride.

(v) The preparation is labeled with adequate directions for use for the temporary relief of itching and scaling due to dandruff.

(vi) The label bears a conspicuous warning to keep the drug out of the reach of children.

(28) Tyloxapol (an alkylaryl polyether alcohol) and benzalkonium chloride ophthalmic preparations meeting all the following conditions:

(i) The tyloxapol and benzalkonium chloride are prepared, with other appropriate ingredients which are not drugs limited to prescription sale under the provisions of section 503(b)(1) of the act, as a sterile, isotonic aqueous solution suitable for use in self-medication on eye prostheses.

(ii) The preparation is so packaged as to volume and type of container as to afford adequate protection and be suitable for self-medication with a minimum risk of contamination of the solution during use. Any dispensing unit is sterile and so packaged as to maintain sterility until the package is opened.

(iii) The tyloxapol, benzalkonium chloride, and other ingredients used to prepare the isotonic aqueous solution meet their professed standards of identity, strength, quality, and purity.

(iv) An application pursuant to section 505(b) of the act is approved for the drug.

(v) The preparation contains 0.25 percent of tyloxapol and 0.02 percent of benzalkonium chloride.

(vi) The label bears a conspicuous warning to keep the drug out of the reach of children and the labeling bears, in juxtaposition with the dosage recommendations, a clear warning that if irritation occurs, persists, or increases, use of the drug should be discontinued and a physician consulted. The labeling includes a statement that the dropper or other dispensing tip should not touch any surface, since this may contaminate the solution.

(29) [Reserved]

(b) [Reserved]

[39 FR 11680, Mar. 29, 1974, as amended at 42 FR 36994, July 19, 1977; 52 FR 15892, Apr. 30, 1987; 52 FR 30055, Aug. 12, 1987; 55 FR 31779, Aug. 3, 1990; 57 FR 58374, Dec. 9, 1992; 58 FR 49898, Sept. 23, 1993; 59 FR 4218, Jan. 28, 1994; 60 FR 52507, Oct. 6, 1995]

## Subpart D—Records and Reports

### §310.303 Continuation of long-term studies, records, and reports on certain drugs for which new drug applications have been approved.

(a) A new drug may not be approved for marketing unless it has been shown to be safe and effective for its intended use(s). After approval, the applicant is required to establish and maintain records and make reports related to clinical experience or other data or information necessary to make or facilitate a determination of whether there are or may be grounds under section 505(e) of the act for suspending or withdrawing approval of the application. Some drugs, because of the nature of the condition for which they are intended, must be used for long periods of time—even a lifetime. To acquire necessary data for determining the safety and effectiveness of long-term use of such drugs, extensive animal and clinical tests are required as a condition of approval. Nonetheless, the therapeutic or prophylactic usefulness of such drugs may make it inadvisable in the public interest to delay the availability of the drugs for widespread clinical use pending completion of such long-term studies. In such cases, the Food and Drug Administration may approve the new drug application on condition that the necessary long-term studies will be conducted and the results recorded and reported in an organized fashion. The procedures required by paragraph (b) of this section will be followed in order to list such a drug in §310.304.

(b) A proposal to require additional or continued studies with a drug for which a new drug application has been approved may be made by the Commissioner on his own initiative or on the petition of any interested person, pursuant to part 10 of this chapter. Prior

to issuance of such a proposal, the applicant will be provided an opportunity for a conference with representatives of the Food and Drug Administration. When appropriate, investigators or other individuals may be invited to participate in the conference. All requirements for special studies, records, and reports will be published in § 310.304.

[39 FR 11680, Mar. 29, 1974, as amended at 41 FR 4714, Jan. 25, 1976; 42 FR 15674, Mar. 22, 1977]

**§ 310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.**

(a) *Scope.* FDA is requiring manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved new drug or abbreviated new drug application to establish and maintain records and make reports to FDA of all serious, unexpected adverse drug experiences associated with the use of their drug products. Any person subject to the reporting requirements of paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(b) *Definitions.* The following definitions of terms apply to this section:—

*Adverse drug experience.* Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

*Disability.* A substantial disruption of a person's ability to conduct normal life functions.

*Life-threatening adverse drug experience.* Any adverse drug experience that places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse drug experience as it occurred, i.e., it does not include

an adverse drug experience that, had it occurred in a more severe form, might have caused death.

*Serious adverse drug experience.* Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

*Unexpected adverse drug experience.* Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(c) *Reporting requirements.* Each person identified in paragraph (c)(1)(i) of this section shall report to FDA adverse drug experience information as